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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,288	12/12/2003	Makoto Kaibara	P24684	2562

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,288	KAIBARA ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/861,708.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0-0.

DETAILED ACTION

1. Applicant's preliminary amendment received December 12, 2003 is acknowledged.

Claims 1-24 are pending in the instant application.

2. Applicant's election with traverse of Group I, claims 1-7, drawn to factor IX-activating protein and compositions comprising said protein, in the reply filed on April 7, 2005 is acknowledged. The traversal is on the ground that there is no search burden involved in simultaneously searching all pending product and method claims and inventions. This is not found persuasive because of the reasons set forth in the restriction requirement mailed March 7, 2005.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 8-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction requirement in the reply filed on April 7, 2005.

4. Applicant's IDS submitted March 12, 2004 is acknowledged. Non-patent literature documents 7 (Sakamoto et al.) and 8 (Fuji et al.) have only been considered to the extent of the English language abstract. Documents 2 (Kaibara et al.) and 11

(Nakamura et al.) have been lined through and not considered because English language translations of these Japanese language documents have not been provided.

Specification

5. The disclosure is objected to because of the following informalities:

A) The table on page 31 is not identified with a number, and there is more than one table in the specification (Table 1 is found on page 33). Appropriate numbering of the tables in the specification will avoid confusion.

B) The sequences disclosed in the table on page 31 are not identified by SEQ ID numbers. Applicant is advised that the specification must comply with the Sequence Rules as set forth in 37 CFR 1.821-1.825. These rules require an appropriate SEQ ID NO: for each disclosed sequence. Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 and correct any deficiencies that may be uncovered by such a review.

C) Figure 10 contains an amino acid sequence not identified in the figure or brief description of the drawings by a SEQ ID number.

D) Glycosylation is misspelled in Figure 14.

E) The text of the middle of the second paragraph of page 30 should be amended to read SEQ ID NO:4 rather than the current SEQ ID NO.4. .

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

6. Claim 1 is objected to because of the following informalities:

A) It is customary for a claim to contain a colon as part of the recitation of a sequence identifier (i.e., SEQ ID NO:4, rather than the period currently found in the claim (SEQ ID NO.4).

B) Members of a Markush group are generally separated with a comma, not a semicolon as is currently recited at the ends of lines 3, 5, and 6 of claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed a factor IX-activating enzyme that has an amino acid sequence of SEQ ID NO:4. The term "has" in relation to SEQ ID NO:4 does not appear to be clearly defined by the specification, and as such the examiner views the term "has" as being equivalent to "comprising", thus allowing for the addition of amino acid sequence to either or both ends of SEQ ID NO:4. The specification refers to factor IX-activating enzyme as erythroelastase-IX (EE-IX), and indicates that it has an apparent molecular weight of 29kDa, contains two glycosylation sites, and differs in sequence from neutrophil elastase by the addition of an arginine residue at the C-terminal end of the enzyme (see particularly the brief description of Figure 14 on page 8, the two paragraphs on page 30, and Figure 14). Thus the enzyme EE-IX is 219 amino acids long, and its sequence consists of SEQ ID NO:4 (see particularly the second full paragraph of page 27 and the middle of the second paragraph of page 30).

The sequence of EE-IX was obtained by a combination of mass spectroscopy of cleaved peptide fragments and Edman degradation, with the peptide sequences and masses of many fragments of EE-IX provided in the table found page 31 (see particularly the paragraph that spans pages 26 and 27, the first two full paragraphs of page 27, the second paragraph on page 30 and page 31). As previously stated, the only sequence difference between EE-IX and neutrophil elastase that appears to be disclosed in the specification is that the sequence of EE-IX is longer by one arginine residue at the C-terminus of the enzyme.

A sequence database search of SEQ ID NO:4 reveals that human neutrophil elastase is the best match, but it does not match 100% because position 80 of SEQ ID NO:4 is a threonine (T) while the corresponding position in neutrophil elastase is a tyrosine (Y) (see enclosed copy of search notes). Neutrophil elastase is synthesized as a longer polypeptide that is enzymatically cleaved to its mature length of 218 amino acids, and an alternate name for neutrophil elastase is medullasin (Okano et al., (1987) J. Biochem 102:13-16, see entire document, particularly the penultimate paragraph on page 16, Result 1 of the enclosed sequence search notes, and Wei et al., FEBS Lett. (1988) 234:367-373, see entire document, particularly Table 2 and the right column of page 369). The C-terminal amino acid of the mature form of neutrophil elastase is generally reported as being a glutamine (Q), but Okano et al. report the last residue to be an arginine (R) (see particularly Figure 2b of Okano et al. on page 15, and Wei et al., the right column of page 369). As such, it appears that the amino acid sequence of elastase can end either at a glutamate (Q) residue (corresponding to position 218 of

SEQ ID NO:4) or at an arginine residue (R) (corresponding to position 219 of SEQ ID NO:4). As such, the inclusion of an additional amino acid to the C-terminal end of EE-IX does not appear to make it a different molecule from neutrophil elastase. Applicant has indicated that another difference between EE-IX and neutrophil elastase is that EE-IX is glycosylated at two positions while neutrophil elastase is glycosylated at three positions (see particularly Figure 14). Neutrophil elastase (and EE-IX since their sequences are identical) has three potential glycosylation sites, but only two sites are actually used (see particularly the ultimate paragraph of Okano et al., the first full paragraph of the left column of page 370 of Wei et al., and Table 2 of Wei et al., and note that the amino acid sequence numbering is different among the papers, even though the sequence is the same). As such, applicant is incorrect in stating that neutrophil elastase is glycosylated at three sites since only two, the same two as in EE-IX, are actually used.

Therefore, it appears that EE-IX is neutrophil elastase. However, the specification discloses that SEQ ID NO:4 is EE-IX, and SEQ ID NO:4 does not align perfectly with neutrophil elastase due to the presence of a threonine (T) instead of a tyrosine (Y) at position 80 of SEQ ID NO:4. Inspection of the sequencing data disclosed in the table on page 31 reveals that the fragment containing residue 80 (fragment 75-115, whose partial sequence is shown) **does not contain a threonine (T) at position 80**. The amino acid at position 80 is tyrosine (Y), just what would be predicted from the prior art sequence of neutrophil elastase (see enclosed sequence search notes). Since the sequence disclosed as SEQ ID NO:4 was compiled from peptide sequencing data, and the peptide sequence data provided in the specification does not support the

inclusion of a threonine (T) instead of a tyrosine (Y) at position 80, it appears that an error was made in the compilation of the data to generate SEQ ID NO:4. As such, the polypeptide encoded by SEQ ID NO:4 **does not exist in nature**. Further evidence concerning the sequencing error contained in SEQ ID NO:4 is contained in applicant's post filing peer-reviewed journal publication wherein it is disclosed that "The amino acid sequence of EE-IX is in accord with that of neutrophil elastase" (see Iwata et al. Biochem Biophys Res Commun. (2004) 316:65-70, see entire document, particularly Table 1 and the first and second paragraphs of the Discussion section on page 69).

All of applicant's experiments utilized purified EE-IX (neutrophil elastase) rather than the polypeptide of SEQ ID NO:4, and there is no indication that applicant has ever synthesized the protein of SEQ ID NO:4 or that SEQ ID NO:4 has the properties and characteristics of EE-IX (neutrophil elastase). Methods of purifying EE-IX are taught on pages 24 and 25, but since these methods rely on obtaining EE-IX from erythrocyte membranes, they cannot be used to make the polypeptide of SEQ ID NO:4 since the polypeptide of SEQ ID NO:4 does not occur naturally. It is known that mutations, including single amino acid substitutions, of neutrophil elastase are associated with human disease states, with said mutations leading to conformational changes in the molecule that alter its biological activity (Dale et al., Blood (2000) 96:2317-2322, see entire document, particularly Table 1, Figure 4, and the last paragraph of the right column of page 2320). It appears that the only information disclosed by applicant about how to make or use SEQ ID NO:4 is the sequence of SEQ ID NO:4 itself. As such there

is no data to support, or motivation to put, the polypeptide of SEQ ID NO:4 in a medicine destined for *in vivo* use as recited in claims 5 and 6.

Since the specification provides no guidance or working examples concerning how to make or use the polypeptide of SEQ ID NO:4 and since the prior art teaches that even single amino acid changes in neutrophil elastase lead to alterations in biological activity, a skilled artisan would need to conduct additional research before being able to make and use the polypeptide of SEQ ID NO:4.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 18, 2005

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